Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

Claims 1-113 are cancelled.

114. (Currently Amended) A method of treating diabetes mellitus in a human patient in need of such treatment, said method comprising:

orally administering to the human patient between about 0.05 and 10 mg per kilogram body weight of an ~~effective amount of a~~ insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:
X is a moiety which forms an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;
m is between 1 and 24;
n is between 1 and 50; and
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the human patient within one hour ~~of~~ prior to ingestion of a meal or contemporaneously with ingestion of a meal by the human patient in order to treat diabetes mellitus in the human patient, wherein the effective amount of the conjugate of Formula III is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

115. (Previously Presented) The method of Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

~~116.~~ Claim 116 is cancelled.

117. (Previously Presented) The method of Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

118. (Previously Presented) The method of Claim 114, wherein the oral administration of the effective amount of the conjugate of Formula III stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

119. (Currently Amended) The method of Claim 114, wherein the conjugate of Formula III clears the bloodstream of the human patient within about 4 hours following administration.

120. (Currently Amended) The method of Claim 114, wherein the administration of the effective amount of the conjugate of Formula III reduces hepatic glucose production in the human patient by at least about 25 percent when compared to hepatic glucose production in the human patient without administration.

121. (Previously Presented) The method of Claim 120, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

122. (Currently Amended) The method of Claim 114, wherein the conjugate of Formula III is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the human patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the human patient.

123. (Currently Amended) The method of Claim 114, wherein the conjugate of Formula III is orally administered less than about one hour prior to ingestion of a meal by the human patient.

124. (Currently Amended) The method of Claim 114, wherein the conjugate of Formula III is orally administered substantially contemporaneously with the ingestion of a meal by the human patient.

125. (Currently Amended) The method of Claim 114, wherein the conjugate of Formula III is orally administered less than about one hour after ingestion of a meal by the human patient.

126. (Previously Presented) The method of Claim 114, wherein the insulin polypeptide is insulin.

127. (Previously Presented) The method of Claim 126, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

128. (Previously Presented) The method of Claim 114, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; and Ala^{B28} Pro^{B29} insulin, human.

129. (Previously Presented) The method of Claim 114, wherein the conjugate of Formula III is present as a substantially monodispersed mixture.

130. (Previously Presented) The method of Claim 114, wherein the conjugate of Formula III is present as a monodispersed mixture.

131. (Previously Presented) The method of Claim 114, wherein the conjugate of Formula III is amphiphilically balanced.

132. (Previously Presented) The method of Claim 114, wherein the effective amount of the conjugate of Formula III is present in a pharmaceutical composition.

133. (Previously Presented) The method of Claim 114, wherein m is between 3 and 16.

134. (Previously Presented) The method of Claim 114, wherein m is between 4 and 14.

135. (Previously Presented) The method of Claim 114, wherein m is between 5 and 10.

136. (Previously Presented) The method of Claim 114, wherein n is between 3 and 18.

137. (Previously Presented) The method of Claim 114, wherein n is between 4 and 14.

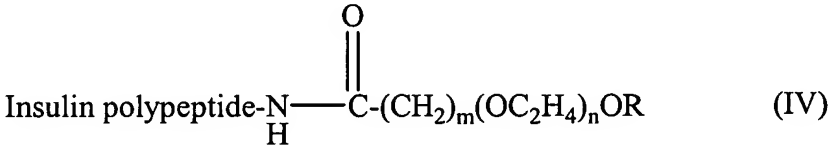
138. (Previously Presented) The method of Claim 114, wherein n is between 5 and 10.

139. (Previously Presented) The method of Claim 114, wherein R is lower alkyl.

140. (Previously Presented) The method of Claim 114, wherein R is C_1 to C_3 alkyl.

141. (Previously Presented) The method of Claim 114, wherein R is methyl.

142. (Previously Presented) The method of claim 114, wherein the insulin polypeptide-oligomer conjugate comprises the structure of Formula IV:



$$\text{Insulin polypeptide-}\underset{\underset{H}{|}}{N}\text{---}\overset{\overset{O}{\|}}{C}\text{-}(CH_2)_m(OC_2H_4)_nOR \qquad \text{(IV)}$$

143. (Previously Presented) The method of Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 30 minutes of administration.

144. (Previously Presented) The method of Claim 142, wherein the effective amount of the conjugate of Formula IV is between about 0.05 and about 10 mg per kilogram body weight.

145. (Previously Presented) The method of Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV provides a maximum insulin drug concentration in peripheral blood within about 60 minutes after administration.

146. (Previously Presented) The method of Claim 142, wherein the oral administration of the effective amount of the conjugate of Formula IV stabilizes peripheral glucose concentration to within

about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

147. (Currently Amended) The method of Claim 142, wherein the conjugate of Formula IV clears the bloodstream of the human patient within about 4 hours following administration.

148. (Currently Amended) The method of Claim 142, wherein the administration of the effective amount of the conjugate of Formula IV reduces hepatic glucose production in the human patient by at least about 25 percent when compared to hepatic glucose production in the human patient without administration.

149. (Previously Presented) The method of Claim 148, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

150. (Currently Amended) The method of Claim 142, wherein the conjugate of Formula IV is orally administered such that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the human patient is hepatically absorbed within about 120 minutes after ingestion of the meal by the human patient.

151. (Currently Amended) The method of Claim 142, wherein the conjugate of Formula IV is orally administered less than about one hour prior to ingestion of a meal by the human patient.

152. (Currently Amended) The method of Claim 142, wherein the conjugate of Formula IV is orally administered substantially contemporaneously with the ingestion of a meal by the human patient.

153. (Currently Amended) The method of Claim 142, wherein the conjugate of Formula IV is orally administered less than about one hour after ingestion of a meal by the human patient.

154. (Previously Presented) The method of Claim 142, wherein the insulin polypeptide is insulin.

155. (Previously Presented) The method of Claim 154, wherein the oligomer is coupled to the lysine at the B29 position of the insulin.

156. (Currently Amended) The method of Claim 142, wherein the insulin polypeptide is an insulin analog selected from the group consisting of Gly^{A21} insulin, human; Gly^{A21} Gln^{B3} insulin, human; Ala^{A21} insulin, human; Ala^{A21} Gln^{B3} insulin, human; Gln^{B3} insulin, human; Gln^{B30} insulin, human; Gly^{A21} Glu^{B30} insulin, human; Gly^{A21} Gln^{B3} Glu^{B30} insulin, human; Gln^{B3} Glu^{B30} insulin, human; Asp^{B28} insulin, human; Lys^{B28} insulin, human; Leu^{B28} insulin, human; Val^{B28} insulin, human; Ala^{B28} insulin, human; Asp^{B28} Pro^{B29} insulin, human; Lys^{B28} Pro^{B29} insulin, human; Leu^{B28} Pro^{B29} insulin, human; Val^{B28} Pro^{B29} insulin, human; and Ala^{B28} Pro^{B29} insulin, human.

157. (Previously Presented) The method of Claim 142, wherein the conjugate of Formula IV is present as a substantially monodispersed mixture.

158. (Previously Presented) The method of Claim 142, wherein the conjugate of Formula IV is present as a monodispersed mixture.

159. (Previously Presented) The method of Claim 142, wherein the conjugate of Formula IV is amphiphilically balanced.

160. (Previously Presented) The method of Claim 142, wherein the effective amount of the conjugate of Formula IV is present in a pharmaceutical composition.

161. (Previously Presented) The method of Claim 142, wherein m is between 3 and 16.

162. (Previously Presented) The method of Claim 142, wherein m is between 4 and 14.

163. (Previously Presented) The method of Claim 142, wherein m is between 5 and 10.

164. (Previously Presented) The method of Claim 142, wherein n is between 3 and 18.

165. (Previously Presented) The method of Claim 142, wherein n is between 4 and 14.

166. (Previously Presented) The method of Claim 142, wherein n is between 5 and 10.

167. (Previously Presented) The method of Claim 142, wherein R is lower alkyl.

168. (Previously Presented) The method of Claim 142, wherein R is C_1 to C_3 alkyl.

169. (Previously Presented) The method of Claim 142, wherein R is methyl.

Claims 170-207 are cancelled.

208. (Currently Amended) A method of treating diabetes mellitus in a human patient in need of such treatment, said method comprising:
orally administering to the human patient an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:
X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;
m is between 1 and 24;
n is between 1 and 50; and
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to treat diabetes mellitus in the human patient, wherein the effective amount of the insulin polypeptide-oligomer conjugate is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of administration.

209. (Currently Amended) A method of treating diabetes mellitus in a human patient in need of such treatment, said method comprising:

orally administering to the human patient an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:
X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-

carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;
m is between 1 and 24;
n is between 1 and 50; and
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the human patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide-oligomer conjugate is administered so that it stabilizes peripheral glucose concentration to within about +/- 50 percent of an average peripheral glucose concentration measured over about a one hour time period beginning within about 30 minutes after administration.

210. (Currently Amended) A method of treating diabetes mellitus in a patient in need of such treatment, said method comprising:

orally administering to the human patient between about 0.05 and 10 mg per kilogram body weight of an ~~effective amount of a~~ insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:
X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;
m is between 1 and 24;
n is between 1 and 50; and
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the human patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide-oligomer conjugate is administered so that it reduces hepatic

glucose production in the patient by at least about 25 percent when compared to hepatic glucose production in the human patient without administration.

211. (Previously Presented) The method of Claim 210, wherein the reduction in hepatic glucose production occurs within about 90 minutes after administration.

212. (Currently Amended) A method of treating diabetes mellitus in a human patient in need of such treatment, said method comprising:

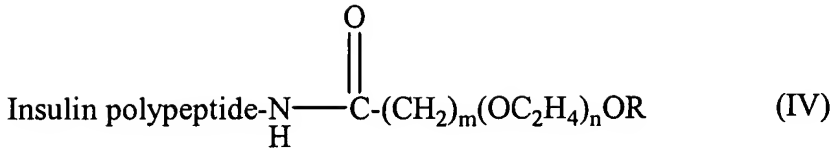
orally administering to the human patient between about 0.05 and 10 mg per kilogram body weight of an effective amount of a insulin polypeptide-oligomer conjugate comprising the structure of Formula III:

$$\text{Insulin polypeptide}\text{——}X(CH_2)_m(OC_2H_4)_nOR \qquad \text{(III)}$$

wherein:
X is an ester moiety, a thio-ester moiety, an ether moiety, a carbamate moiety, a thio-carbamate moiety, a carbonate moiety, a thio-carbonate moiety, an amide moiety, a urea moiety, or a covalent bond;
m is between 1 and 24;
n is between 1 and 50; and
R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety;

to the human patient in order to treat diabetes mellitus in the patient, wherein the effective amount of the insulin polypeptide-oligomer conjugate is administered so that at least about 25 percent of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed within about 120 minutes of ingestion of the meal by the human patient.

213. (Currently Amended) The method of claim 209 wherein the insulin polypeptide-oligomer conjugate comprises the structure of Formula IV:



(IV)

wherein:

m is between 1 and 24;

n is between 1 and 50; and

R is an alkyl moiety, a sugar moiety, cholesterol, adamantane, an alcohol moiety, or a fatty acid moiety; and is administered so that it provides an insulin drug concentration in portal vein blood between about 10 and 1,000 U/ml within about 60 minutes of oral administration to the human patient.

Claims 214-230 are cancelled.